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Abdominal pressure and gastrointestinal function: an inseparable couple?

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Abstract

Evaluating the degree of organ dysfunction is a cornerstone in distinguishing patients with critical illness from those without. However, evaluation of the gastrointestinal function in critically ill patients is not unified, and is still largely based on subjective clinical evaluation. Although intra-abdominal pressure has been proposed as a parameter to facilitate monitoring of abdominal compartment in critical illness, the interactions between intra-abdominal pressure and gastrointestinal function are poorly clarified.

The aim of this current review is to describe interactions and associations between gastrointestinal dysfunction and intra-abdominal pressure from a pathophysiological and clinical point of view.

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Key words: intra-abdominal hypertension; gastrointestinal function; gastrointestinal failure; acute gastrointestinal injury; critical illness; microbiome

Assessing organ function and dysfunction is important in critically ill patients. Recently published new sepsis guidelines have incorporated organ dysfunction in sepsis definitions [1], whereas work in refining definitions of different organ dysfunctions [2, 3] is ongoing. Even if not always easy at the bedside, it is usually possible to categorize organ function as normal or abnormal for most organ systems. At the same time, despite several efforts [4, 5], evaluating gastrointestinal (GI) function in critically ill patients is not unified, and is still largely based on subjective clinical evaluation [6–8]. The term "Acute Gastrointestinal Injury" (AGI) has been recently proposed to describe GI dysfunction as a part of multiple organ failure (MOF) [7]. Intra-abdominal pressure (IAP) has been proposed as a measurable parameter to facilitate monitoring of GI function in critical illness [8, 9]. IAP is not directly related to GI function but is a relatively objective and reproducible numerical parameter that allows the indirect detection of changes that occur within in abdominal compartment. IAP is the steady state pressure conceived within the abdominal cavity, that can be measured via the bladder at end-expiration in the supine position zeroed at the level where the midaxillary line crosses the iliac crest [9]. Intra-abdominal hypertension (IAH) is defined as a sustained increase of IAP equal to or above 12 mm Hg [9]. IAH has been shown to influence the outcome of critically ill patients, whereas the role of the GI system in the development, as well as in the outcome of IAH, is poorly clarified [8, 10–12].

The aim of this current review is to describe possible interactions and associations between GI dysfunction and IAP from a pathophysiological and clinical point of view.

METHODS

MEDLINE and PubMed searches were performed using the search terms 'gastrointestinal symptoms', 'gastrointestinal dysfunction', 'acute gastrointestinal injury', 'intra-abdominal pressure', 'intra-abdominal hypertension', 'intra-abdominal hypertension', 'abdominal perfusion', 'micriobiome', 'abdominal compartment syndrome' and 'critically ill' OR 'intensive care' OR 'critical care' OR 'critical illness'. The reference lists of identified papers were screened to identify other relevant papers.

RESULTS AND DISCUSSION

ANATOMICAL AND PHYSIOLOGICAL BACKGROUND

ANATOMY OF THE ABDOMINAL COMPARTMENT AND GI SYSTEM

IAH develops when too much intra-abdominal volume (IAV) occupies the semi-confined space referred to as the abdominal compartment. As the GI system is a major space occupant in the abdominal compartment, it is important to clarify its role in the development of IAH and *vice versa*.

The abdominal compartment is surrounded by the diaphragm, spine, costal arch, abdominal wall and pelvis. It contains multiple solid and hollow organs, adipose tissue and major blood vessels, which can be located intra- and/or retroperitoneally. Not limited by the anatomical borders, IAH affects both intra- and extraperitoneal organs and tissues.

The GI system consists of a series of hollow organs (GI tract), with a total length of around 5 m [13] into which accessory organs add their secretions. These accessory organs, including the liver, gall bladder and pancreas, also occupy considerable space. The space-occupying effect of the GI tract is variable and depends on the content of food, stool, secretions and gas, as well as the underlying disease state (e.g. bowel oedema).

PHYSIOLOGY OF THE GI SYSTEM

Although energy uptake is the most obvious, it is not the only function of the GI tract by far. Barrier, immunologic, exocrine and endocrine functions are equally important. Upholding GI functions depends on adequate GI motility, exocrine secretions and local tissue perfusion. GI physiology in detail is beyond the scope of the current review and has been covered elsewhere [14–16]. However, the course and role of GI dysfunctions in critical illness is not clearly understood and GI function monitoring tools are lacking.

GI MOTILITY, DIGESTION AND ABSORPTION

The functions of the GI system are modulated by complex myogenic, neural, and humoral mechanisms.

GI motility assists with mixing (non-propulsive movements), propulsion (progressive wave of relaxation, followed by contraction), retropulsion (reflux) and storage. The motor activity pattern of the GI system differs between fasting and fed states and both appear to be profoundly disturbed in critical ill patients [14].

The stomach stores ingesta and has substantive motor, secretory, humoral, and digestive functions. The small bowel absorbs nutrients, fluids, electrolytes, and secretes peptides. Pancreatic secretions and bile enter the duodenal lumen, assisting digestion. The large bowel absorbs water and electrolytes, as well as the remaining unabsorbed carbohydrates, stores luminal contents until evacuation and secretes fluid and electrolytes.

IMMUNOLOGICAL AND BARRIER FUNCTIONS

Intact gut mucosa provides a physical barrier while gastric acid, intestinal mucin, bile, and peristalsis are the non-immunological elements of gut protection against pathogens [14]. The immunological protection gut-associated lymphoid tissue (GALT) takes up orally ingested antigens that activate lymphocytes, able to secrete IgA in response to prolonged antigen exposure and allowing "oral tolerance" [15].

BLOOD SUPPLY TO THE INTESTINES

The coeliac artery is responsible for the main blood flow to stomach, pancreas, and spleen. The small and large intestine are supplied from superior and inferior mesenteric arteries, with interconnections between the arcading branches providing multiple collateral pathways. Venous drainage from the stomach, intestines, pancreas, and spleen is via the portal vein system [16].

The fountain-like arrangement of microvessels in the villi facilitates the counter-current exchange of solutes, moving from arteriole to venule without traversing the entire length of the villus [16]. At the same time, this arrangement makes the tip of the villus highly susceptible to damage from hypoxia and/or hypotension (Fig. 1) [14, 17]. The oxygen extraction rate can be increased remarkably from 20% at rest in order that temporary reductions in blood flow can be tolerated. Longer periods of intestinal hypoperfusion may result in mucosal sloughing at the tip of the villi. This sloughing disrupts the barrier, which is a putative mechanism leading to MOF [14]. As the tips of intestinal villi are essential for absorption of nutrients, such injury of the villi can lead to impaired absorption and feeding intolerance [18].

Sympathetic activity directly constricts splanchnic vessels. Parasympathetic activity stimulates intestinal motility

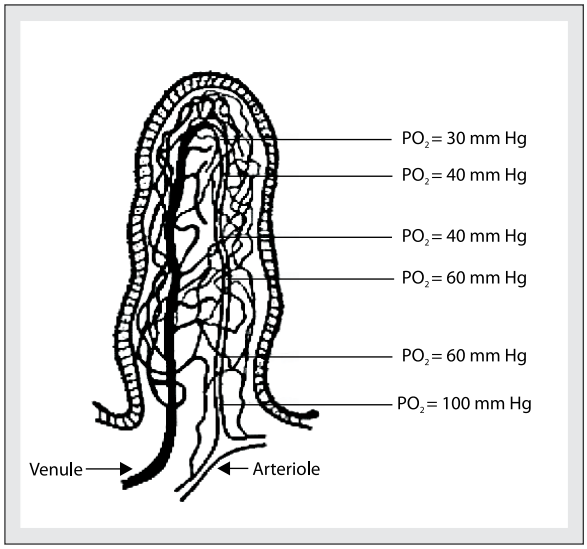

Figure 1. Arrangement of micro vessels in the intestinal villi, showing the progressive decrease in arteriolar PO_2 towards the tip of the villi [17], used with permission of the authors

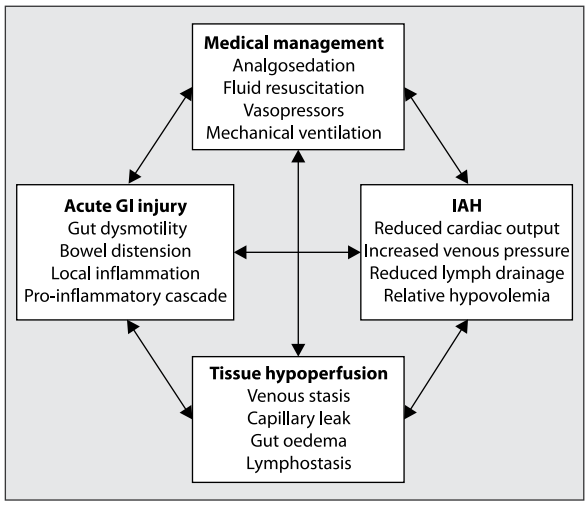

Figure 2. Pathophysiological mechanisms shared between GI dysfunction and IAH

and secretion and increases metabolism, thereby indirectly increasing local tissue perfusion. A reduction in splanchnic blood flow leads to the production of vasodilatory metabolites.

PATHOPHYSIOLOGICAL MECHANISMS CONNECTING GI DYSFUNCTION AND IAH

There is still some debate whether IAH per se increases mortality or is just another marker of the severity of the disease [19, 20]. Some of the differences found in the literature regarding the effect on outcome may be explained with the duration and degree of IAH being important factors in determining the effect of IAP on organ dysfunction and outcome [20, 21–23]. Frequently, studies categorize patients has having IAH without assessing either the degree of IAH, its duration or the timeframe of its development. At the same time, the magnitude of elevation in IAP above baseline, the acuteness (the "speed" of increase in IAP over time) and the duration of exposure to IAH, are known to be major determinants of related organ dysfunction. Chronic exposure to slowly increasing IAP (e.g. ascites in patients with liver cirrhosis, pregnancy, ovarian tumours) allows time for physiological adaptation, thereby reducing systemic consequences. However, IAH has been suggested as a mechanism leading to pre-eclampsia when adaptation to an increase in IAH appears insufficient [24].

In adults, a cut-off value of 12 mm Hg IAP has been chosen as observational data shows that mortality in critically ill patients increases above this threshold [10, 11, 21]. Signs of organ dysfunction, duration of mechanical ventilation, ICU length of stay and ICU mortality are increased in most studies [10, 11, 25].

Shocked patients with IAH (IAP ≥ 12 mm Hg) were found to have a higher rate of acute kidney injury (AKI) than those without IAH [23] and this finding was thought to be attributable to a decreased abdominal perfusion pressure (APP = MAP – IAP) in such patients.

The pathophysiological mechanisms shared between GI dysfunction and IAH are shown in Figure 2.

The following mechanisms linking IAP and GI function are discussed in detail further on:

1. The effect of increasing intra-abdominal volume on the development of IAH.
2. Effects of IAH on systemic blood flow and vascular resistance.
3. The effect of IAH on splanchnic organ perfusion.
4. Abdominal lymph flow in critically ill patients with IAH.
5. Intestinal blood flow and enteral nutrition.
6. Effects of IAH on tissue perfusion and microcirculation.
7. The effect of vasopressors on splanchnic perfusion in the setting of IAH.
8. The effect of IAH and critical illness on gut microbiome and gut permeability.
9. Intestinal oedema formation in critically ill patients and in patients with IAH.
10. Bowel distension and IAH.

THE EFFECT OF INCREASING INTRA-ABDOMINAL VOLUME ON THE DEVELOPMENT OF IAH

If intra-abdominal volume (IAV) increases, IAP starts to increase as well. The increase in IAP depends on the magnitude of additional IAV, baseline IAP and abdominal compliance [26–29]. Abdominal compliance — a measure of the ease of abdominal expansion — differs between individuals (e.g. age) and conditions (e.g. chronic ascites, massive fluid resuscitation, burns) and plays a major role in

whether a patient develops IAH or abdominal compartment syndrome (ACS) [9, 26–29].

When increasing IAV, three different phases in an abdominal pressure-volume curve may be distinguished: 1) the reshaping phase, where abdominal configuration changes (ellipsoid to circular circumference) along with a minimal change in IAP; 2) the stretching phase, with elastic elongation of the abdominal wall and diaphragmatic tissue, where IAP increases in parallel with IAV; and 3) the pressurizing phase, with large increases in IAP with relatively small additional IAV [26, 27]. Stretching capacity is dependent not only on abdominal wall structure and compliance but also on the shape, elasticity and function of the diaphragm [26]. Thoraco-abdominal interactions may also play important role in development, as well as in the consequences of IAP, especially in critically ill patients [30]. Next to reshaping and stretching capacity, these dynamic changes are dependent on the resting (baseline) values of IAV and IAP, being different in each patient. Repeated measurements of IAP (or continuous IAP monitoring [31, 32]) are pivotal for following any acute changes taking place in the abdominal compartment.

EFFECTS OF IAH ON SYSTEMIC BLOOD FLOW AND VASCULAR RESISTANCE

IAH has a biphasic hemodynamic effect. Low levels of IAP have been shown to increase blood pressure and cardiac output [32–37]. This increase in cardiac output is thought to result from an increase in venous return as a result of a redistribution of abdominal blood to the thoracic compartment [33, 38]. Higher levels of IAP decrease blood pressure and cardiac output [35, 39]. IAH causes a cranial shift of the diaphragm, thereby increasing intrathoracic pressures. Abdomino-thoracic pressure transmission is estimated to be around 50% of IAP [39]. Static preload parameters such as right atrial pressure and pulmonary artery occlusion pressure are misleadingly elevated [40]. Venous return is reduced due to a compression of the inferior vena cava [33, 38]. The critical opening pressure of the inferior vena cava will depend on IAP, intra-thoracic pressure and fluid status [41].

Systemic vascular resistance is increased, likely due to vascular compression and humoral factors, such as endogenous catecholamines, vasopressin and activated renin-angiotensin pathway [42, 43]. Animal and human research suggests that IAH activates sympathetic nerves in the region of the portal drainage area causing splanchnic vasoconstriction [44, 45].

THE EFFECT OF IAH ON SPLANCHNIC ORGAN PERFUSION

Over the years many different techniques have been suggested to assess hepatosplanchnic perfusion. Doppler flow probes within vessels and transit-time flow probes around vessels are frequently used in animal models to assess blood flow through abdominal vessels, whereas dynamic direct monitoring in patients is not available.

The intra-and retroperitoneal organs are highly vascularised and, in health, a great proportion of the cardiac output is diverted to these organs. For example, the liver and the kidneys receive around 25% and 20% of the cardiac output, respectively [16]. The splanchnic circulation serves as a major reservoir of blood in critical conditions; about half the splanchnic blood volume can be rapidly mobilized [16]. Therefore, these organs are sensitive to hypovolemia and IAH leading to hypoperfusion and organ dysfunction.

Pressure in the abdominal veins increases linearly with rising IAP [46–48]. Abdominal perfusion pressure (APP) is calculated as mean arterial pressure (MAP) – IAP [9]. For a given MAP, APP will inherently decrease with increasing IAP leading to splanchnic hypoperfusion and ischemic lesions. Moreover, the increased abdominal venous pressure in the context of IAH causes a venous backflow pressure comparable to venous congestion that occurs in patients with right heart failure and thereby impairs organ perfusion, even in the face of a preserved MAP [36, 49].

IAH causes a dose-related decrease in abdominal blood flow including the mesenteric artery, the hepatic artery, the portal veins and the renal artery [46, 50–54]. The threshold of IAP causing reductions in regional abdominal blood flow has been shown to vary between 8 and 20 mm Hg and probably reflects the different measurement techniques used (Doppler flow probes, transit-time flow probes) and subjects studied (animals, humans) [46, 53].

ABDOMINAL LYMPH FLOW IN CRITICALLY ILL PATIENTS WITH IAH

The lymphatic system drains and transports excessive interstitial fluid from the GI system to lymphatic ducts which are further drained via the thoracic duct into the systemic circulation at the angle of the left subclavian and internal jugular veins. Importantly, lymph vessels in the gut do not have valves, making the lymph flow dependent on bowel peristalsis (abdominal compartment) and ventilation (thoracic compartment) [55, 56]. Therefore, in critically ill patients with abnormal or missing peristalsis, this clearance of interstitial fluid is impaired. Furthermore, mechanical ventilation with high intra-thoracic pressure (ITP) can affect lymph flow, by impeding lymphatic return, while the concomitant increase in splanchnic venous pressure may result in a net increase in lymph production favouring oedema formation [57, 58].

IAH also reduces abdominal lymph drainage aggravating gut oedema. Lattuada *et al.* [57] found that endotoxin

increased thoracic lymph flow in anesthetised pigs, whereas IAH decreased lymph flow irrespective of whether the pigs were septic or not.

INTESTINAL BLOOD FLOW AND ENTERAL NUTRITION

In healthy subjects, the presence of nutrients in the small intestine augments intestinal blood flow via stimulation of secretion of vasoactive gastrointestinal hormones [17]. The magnitude of this increase in intestinal blood flow is dependent on meal size and the rate of nutrient delivery into the small bowel and can increase up to two-fold (superior mesenteric artery flow) [17]. Such meal-induced splanchnic blood pooling, diverting around 20% of total blood flow to the intestines, results in a temporary "relative systemic hypovolemia" [59]. This "relative systemic hypovolemia" stimulates the baroreceptors to increase sympathetic activity, leading to increase in heart rate and stroke volume, thereby augmenting cardiac output [59], but also leading to a vasoconstriction of the skeletal vasculature [17]. In shocked patients, such food-related increase in splanchnic blood flow may be deleterious due to possible reperfusion injury or "stealing" blood/oxygen from other vital organs such as the heart and brain [17].

It is not clear to what degree and in what situations enteral nutrition may protect against or, on the contrary, exacerbate mesenteric ischemia in critically ill patients [17]. To some degree the delayed gastric emptying found in such patients diminishes the delivery of nutrient to the small intestine, and may attenuate the described reactions [17]. On the other hand, due to impaired absorption of nutrients in the critically ill, undigested carbohydrates and fats may remain in the distal small intestine, thereby sustaining the aforementioned reactions for longer periods. In addition, the presence of unabsorbed nutrient in the bowel can result in fluid shifts, bacterial overgrowth and fermentation, causing bowel distension [17].

EFFECTS OF IAH ON TISSUE PERFUSION AND MICROCIRCULATION

As described above, IAH can reduce abdominal organ blood flow, whereas severe impairment in microcirculation may stay masked during successful stabilization of systemic blood pressure and cardiac output.

Microcirculation is either directly measured or indirectly assessed. Direct measurement of microcirculatory blood flow may be performed by a measured orthogonal polarization spectroscopy (OPS), side stream dark field (SDF) imaging or by Doppler flow meters that penetrate the mucosal surface between 0.5 and 1 mm in depth. Indirect measurements of tissue perfusion include intramucosal tonometry [60, 61] and the indocyanine green clearance rate [62].

There appears to be considerable variation in the effect of IAH on organ and tissue perfusion. Diebel *et al.* [63] demonstrated that exposure to IAH (25 mm Hg) reduced microcirculatory blood flow of the ileal mucosa by around 30%. Olofsson *et al.* [64] measured microcirculatory flow in pigs with IAH and found a dose-dependent general decrease of the splanchnic microcirculation. However, in relation to cardiac output there was a relative sparing of the small bowel and colon mucosal blood flow.

Preliminary data suggest that even mild to moderate IAH can have a negative impact on tissue perfusion and microcirculation [24, 65]. In an animal experiment, the application of 12 mm Hg pneumoperitoneum, together with a positive end-expiratory pressure (PEEP) of 10 cm H_2O, decreased blood flow in the hepatic and mesenteric arteries and portal vein, and impaired the hepatic and intestinal mucosal microcirculation [24]. Impairment in microcirculation through pneumoperitoneum has been confirmed in several other experimental studies [64, 66].

The negative effect of IAH on splanchnic microcirculation appears to be dose-dependent [67]. In an experimental study in rabbits, microvascular blood flow decreased continuously during the application of IAP 15 mm Hg for 6 h, whereas application of IAP 25 mm Hg for 6 h led to dramatic reduction in microcirculatory blood flow (80% reduction from baseline) and intestinal permeability [66]. The authors also demonstrated erosions and necrosis of the jejunal villi, mitochondrial swelling and discontinuity of intracellular tight junctions after prolonged exposure to increased IAP [66]. Leng *et al.* [65] showed adverse effects on intestinal permeability increasing along with gradually elevated IAP, starting already from an IAP of 8–12 mm Hg.

Such a dose-dependent relationship between IAP and microcirculatory gastric mucosal oxygen saturation has also been demonstrated in humans undergoing laparoscopy [68]. However, in humans, an IAP in the range of 12 to 15 mm Hg for a short time period, as used during laparoscopic procedures, is unlikely to cause clinically manifesting organ dysfunction, whereas prolonged exposure to higher IAP levels is more likely to cause tissue hypoperfusion and damage at a cellular level [24].

Dubin *et al.* [69] showed that fluid resuscitation was able to normalize systemic and splanchnic perfusion, as well as intestinal serosal microvascular blood flow but not ileal villi blood flow, which may explain the persistence of intramucosal acidosis in endotoxemic sheep after fluid resuscitation.

Recent findings revealed that changes in abdominal tissue metabolism, assessed via microdialysis , may occur well before the development of IAH-related organ dysfunction [70, 71].

THE EFFECT OF VASOPRESSORS ON SPLANCHNIC PERFUSION IN THE SETTING OF IAH

Fluid resuscitation may improve blood pressure and cardiac output in patients with IAH but may also further increase IAP, thereby decreasing APP and starting a vicious cycle [72]. Often vasoactive drugs are used to stabilize systemic hemodynamic variables in these patients. There remains the fear that using vasoactive drugs may cause splanchnic ischemic lesions [73].

Just which MAP we should be targeting in the setting of IAH remains unknown. The 2016 'Surviving Sepsis' campaign suggests aiming to maintain an MAP of ≥ 65 mm Hg in the context of septic shock [74]. Previously, an abdominal perfusion pressure (APP = MAP – IAP) of ≥ 60 mm Hg was suggested as a goal of resuscitation [75]. The rationale is to assure sufficient perfusion pressure for the abdominal organs, a concept similar to the well-known cerebral perfusion pressure. However, due to a lack of evidence, no recommendation regarding APP or MAP is currently made by the WSACS [9].

Knowledge of what the best vasoactive/inotropic drug should be preferred in patients with IAH remains unknown. Studies examining the splanchnic effect of vasoactive drugs: 1) are most often performed in animals and not in humans [54, 76–82]; 2) frequently compare such an effect in septic and non-septic conditions [76–78]; and 3) are rarely performed in the setting of IAH [54, 81, 82].

The systemic and splanchnic effects of noradrenaline (NA) appear to differ significantly between septic and non-septic conditions. In healthy sheep, NA increases coronary but not superior mesenteric artery flow [80]. In healthy dogs, NA increases blood pressure and cardiac output, but decreases renal arterial blood flow. However, under septic conditions the effects of NA on blood pressure and cardiac output are blunted, but have been shown to improve renal artery blood flow [78, 79]. Similarly, in septic dogs, NA has been shown to improve MAP, CO and hepatic artery blood flow without reducing renal and mesenteric artery blood flow [76]. In patients with septic shock, NA has been shown to improve splanchnic circulation as assessed by the indocyanine green dilution method [83].

Peng *et al.* [82] studied the hemodynamic effect of NA in the setting of IAH in healthy dogs and in bacteraemic dogs. IAH caused a dose-dependent decrease in cardiac output and renal blood flow, both in septic and non-septic conditions. NA was able to fully restore this negative effect of IAH only in septic conditions but not in non-septic conditions.

Ferrara *et al.* [54] studied the hemodynamic effect of NA in a healthy sheep model of IAH. While an IAP of 20 mm Hg did not change cardiac output or blood pressure, it decreased superior mesenteric and renal artery blood flow. NA did not restore the flow in the superior mesenteric and renal artery during IAH.

In pigs, dobutamine was found to reverse the IAH-induced reduction in cardiac output and microvascular ileal blood flow, but not the superior mesenteric artery flow [81].

Dopamine has not been shown to have any beneficial effect on splanchnic hemodynamic variables [84].

Compared to noradrenaline, vasopressin was associated with a trend to improved survival in patients with septic shock [85]. A *post hoc* analysis of the VASST trial found that a subgroup of patients had a lower progression rate to renal failure [86]. The physiological rationale is that vasopressin constricts the efferent as opposed to NA predominantly constricting the afferent renal vessel [86]. Vasopressin may also have a different hemodynamic profile, depending on the presence or absence of sepsis. In dogs, vasopressin has been shown to improve renal blood flow only in septic conditions [77]. However promising vasopressin may be, in critically ill patients with septic shock the addition of vasopressin has been shown to increase the gastric PCO_2 gap, suggesting possible splanchnic hypoperfusion [87, 88].

THE EFFECT OF IAH AND CRITICAL ILLNESS ON GUT PERMEABILITY AND GUT MICROBIOME

In animal experiments, IAH has been shown to: 1) increase oxidative stress and free radicals in the splanchnic region [89, 90]; 2) reduce the number and expression of intracellular tight junctions [65, 66]; 3) increase gut permeability measured as an increase in the transfer of marked dextran from the intestinal to the portal vein [65, 66]; 4) increase apoptosis activity in the gut [90]; 5) increase splanchnic neutrophil recruitment [90]; and 6) increase portal venous endotoxin levels [65].

Histological changes of IAH exposure include the formation of mucosal oedema, neutrophil infiltration, mitochondrial swelling and necrosis of the villi [66].

IAH causes bacterial translocation in the basis of splanchnic hypoperfusion and ischemic changes. In rats, as little as 60 min of 15 mm Hg is sufficient to cause bacterial translocation to the mesenteric lymph nodes, liver and spleen [63, 89]. Translocation occurred around 3 hours after exposure and persisted for up to 24 hours after the event [63, 89].

Hypovolemia and high PEEP both appear to aggravate the effects of increased IAP, causing organ damage [91, 92].

The paradigm of sepsis has undergone several major overhauls over the last decades. Pathogens alone are not responsible for multi-organ failure and death. Animal experiments have revealed that survivors and non-survivors of sepsis are similar in terms of bacterial translocation and dissemination [93]. This has led to the immunocentric model of sepsis with the host response to bacterial infections fea-

turing the immune system triggering a cascade of immune reactions that can lead to multi-organ failure and death [93].

The first line of defence against invaders consists of physical barriers such as the mucous membranes of the gastrointestinal tracts. The second line is a rapid defence by the innate immune system acting due to the broad recognition of antigens, mainly by sensing pathogen-associated molecular patterns (PAMP) of carbohydrates and fatty acids located on the surfaces of common pathogens. When a local response spreads systemically the activation of several classes of pattern recognition receptors will generate a "cytokine-storm" [94]. However, very similar molecules are released, mainly from the mitochondria of necrotic cells after trauma, burns, ischemia-reperfusion, pancreatitis, or major surgery. These are called "damage-associated molecular patterns" (DAMP). The aim of the innate response is the eradication of DAMPs and PAMPs, which is followed by an adaptive response with the resolution of the immunological process. The adaptive immune response is based on maturation and proliferation, both influenced by the "cytokine signature" of the innate response. However, in the case of an unbalanced, dysregulated response, the localized process goes out of control and becomes systemic, giving way for impairing the function of distant vital organs [95].

Recently, increasing understanding of our microbiome is starting to change our understanding of sepsis. The microbiome can be defined as the entirety of microbiological flora including commensal and pathogenic bacteria, viruses, and fungi as well as their genes and their gene products (proteins and metabolites) [93].

The majority of our microbiome is located in the gastrointestinal system, chiefly within the colon. The number of colonic microbiome cells has been calculated to be equal to that of human cells with an estimated colonic inner volume of 400 mL and a bacterial density of 10^{11} bacteria per g [96].

The intestinal microbiome is considered to function as a virtual organ responsible for upholding important physiological functions, including: 1) immunological functions; 2) intestinal mucus production; 3) upholding permeability (via tight junctions); and 4) digesting complex plant polysaccharides into acetate and butyrate, an important energy source for colonic epithelial cells [93, 97].

In comparison to healthy patients, the microbiome's composition and function changes in critically ill patients [97]. In case of severe changes, a dysbiosis occurs, a state in which disruption of the local homeostasis causes the microbiome to collapse both in bacterial biomass and in functional output (altered protein expression) [98]. Environmental factors such as pH, iron, phosphate and osmolality can change a friend to foe and bacteria from commensal to pathogen [98].

The main causes for dysbiosis in critically ill patients are as follows: 1) critical illness; 2) nutritional changes; 3) the use of antibiotics; d) gut ischemia; and perhaps 4) the presence of abdominal hypertension [93, 97, 98].

Of note is that around two thirds of critically ill patients receive antibiotics during their ICU stay, causing collateral damage to the microbiota and promoting the growth of pathogens [99]. The consequences of a microbiome failure include the reduction in barrier function through a reduction in mucin production and increased permeability (reduction in tight junctions) [93]. Observational data indicate a strong relationship between previous dysbiosis (due to antibiotic exposure) and increased occurrence of subsequent severe sepsis [100].

It is thought that by correcting dysbosis and restoring a functional microbiome, there will be: 1) a restored intestinal barrier function (tight junction, colonic mucin production); 2) an improved intestinal immune function (IgA production, suppression of immune cell proliferation); 3) a reduction of gut apoptosis; and 4) a reduction of pathogens, both in number and function [98].

Encouraging case reports and observational data of successful faecal transplant in patients with abdominal sepsis and with *Clostridium difficile* infections support the rationale for intervention regarding microbiota [101–103].

Probiotics are living microbes of human origin that when ingested, can colonize the GI tract and provide benefits to the host [104]. Probiotics are being increasingly investigated in critically ill patients and have also been shown to correct dysbiosis and revitalize the microbiome [98]. However, despite some studies and meta-analyses on probiotics to critically ill patients showing promising results (e.g. reduction in infection rates), convincing results on patient outcome are still lacking [98].

In rats, Leng et al. found that 90 min of IAH (20 mm Hg) changed the number and diversity of the microflora [101]. There was a decrease in beneficial species (*Firmicutes, Lactobacilli*) and an increase in pathogens (*Helicobacter, Pseudomonas, Bacteroides*). There was also an increased migration of *Bacteroides* from the colon to the jejunum. They also found a decrease in tight junctions and an increase in toll-like receptors suggesting an association between dysbiosis and increased gut permeability in the setting of IAH.

INTESTINAL OEDEMA FORMATION IN CRITICALLY ILL PATIENTS AND IN PATIENTS WITH IAH

The mechanisms leading to, and aggravating gut oedema in critical illness are as follows: 1) increased interstitial fluid due to generalised and local capillary leak; 2) decreased lymph flow due to impaired GI motility and increased IAP and/or intra-thoracic pressures; 3) IAH leading to venous congestion and splanchnic hypoperfusion.

Capillary leak represents the maladaptive, excessive and undesirable loss of fluid and electrolytes into the interstitium that can generate gut oedema through second and third space fluid accumulation. The term "capillary leak syndrome leading to intestinal oedema" was first described decades ago [105, 106]. However, the term "Global increased permeability syndrome (GIPS) has been proposed more recently to describe an increased permeability throughout the body due to one or more noxious stimuli causing ischaemia-reperfusion injury and activating systemic immune response. This systemic immune response includes the activation of neutrophils and the innate immune system causing the systemic release of cytokines with the end result of systemic capillary leak and multi-organ failure [107]. Concomitantly, capillary leak leads to intravascular hypovolemia, hypotension and reduced cardiac output and is, therefore, commonly treated with fluid resuscitation. Fluid resuscitation itself may further aggravate capillary leak syndrome through the pro-inflammatory effect of intravenous fluids [108]. Fluid resuscitation further aggravates visceral swelling and intestinal oedema, thereby increasing IAV that, depending on abdominal compliance, may cause IAH. However, IAH itself may cause venous congestion and intestinal oedema and, in combination with decreased cardiac output and abdominal perfusion, trigger a vicious cycle of increased use of resuscitation fluids [107]. Moreover, even in an isolated model of IAH without fluid overload and capillary leak, venous hypertension *per se*, with associated venous congestion, leads to intestinal hypoperfusion and subsequent gut oedema.

The dynamics of any underlying condition will determine the course and severity of capillary leak syndrome and the need for continuing fluid resuscitation. With appropriate treatment (e.g. with adequate source control and correct antibiotic treatment in cases of sepsis) shock can be reversed. Generalised and gut oedema due to fluid resuscitation (administered during the capillary leak phase) spontaneously mobilises in most patients. However, in some patients the state of shock persists with on-going GIPS leading to increasing fluid accumulation and organ dysfunction.

Oedema generally increases the distance between vessels and cells, thereby impairing the delivery of oxygen and nutrients to tissue. Gut oedema will increase the distance a nutrient has to travel providing a physical barrier to the absorption of nutrients from the gut into the blood. Accordingly, gut dysfunction is very likely to occur in the presence of tissue oedema.

On the one hand, gut oedema can lead to IAH through an increase in intra-abdominal volume, while, on the other hand, IAH may lead to, or aggravate gut oedema. In the most extreme cases, increased GI fluid sequestration following crystalloid resuscitation can lead to the abdominal compartment syndrome without any other structural pathology in the abdomen [109].

Gut oedema and elevated IAP both decrease tissue oxygenation, impair cell metabolism, increase gut susceptibility to infection, as well as impair gut anastomosis healing [110, 111]. In rabbits, Nessim *et al.* [112] showed that larger volumes of administered crystalloids were associated with weaker bowel anastomoses, increasing the risk of anastomotic leakage.

Data on the direct effect of IAP on gut oedema are scarce. In an interesting study, Uray *et al.* [113] found that the combination of fluid resuscitation and venous hypertension (mimicking IAH) resulted in the highest gut wet-to-dry ratio and gut oedema decreased myosin light chain phosphorylation leading to decreased intestinal contractility. The decrease in contractility may explain why IAH is associated with frequent failure to establish successful enteral nutrition in critically ill patients.

BOWEL DISTENSION AND IAH

Critically ill patients frequently have a varying degree of GI dysfunction, even in the absence of any obvious abdominal pathology. Most often bowel motility is impaired and gut microflora disturbed in such patients, leading to excessive production of gas and bowel distension [17], followed by increase in IAP. If the bowel wall is overstretched, mucosal perfusion decreases and the pro-inflammatory cascade is activated. This leads to increased mural and vascular permeability allowing the translocation of fluid, bacteria and toxins across the bowel wall [17]. Furthermore, gut oedema further exacerbates tissue hypoperfusion.

STUDIES CONNECTING IAP AND CLINICAL SYMPTOMS OF GI DYSFUNCTION

Clinical associations between IAP, GI dysfunction and GI symptoms have been poorly studied. Existing data suggest associations and between the occurrence of GI symptoms, GI dysfunction and IAH. In 398 patients, observed over a total of 2,987 ventilation days, GI symptoms (mainly vomiting, large gastric residuals and absent bowel sounds) occurred in 80% and IAH in 38% of patients. Only 3% of patients with IAH did not have any GI symptoms, whereas 36% of patients presented both IAH and at least one GI symptom during their entire ICU stay [12]. In the 35% of the patients with IAH and GI symptoms, the GI symptoms occurred before they developed IAH; in 11% IAH occurred before they developed GI symptom(s); while in 54% both IAH and GI symptoms were noticed simultaneously [12].

A higher prevalence of feeding intolerance (FI) in patients with IAH has been demonstrated in several studies [4, 114]. Bejarano *et al.* [114] showed that baseline IAP together with an APACHE II score may predict FI. The authors proposed an interesting combination of IAP and

APACHE II score in order to predict FI. Indeed, the results suggest that patients with higher APACHE II scores are more vulnerable to IAP induced FI [114]. In many other studies, higher severity of illness scores have been reported in patients with IAH, as well as in patients with GI dysfunction and FI [4, 19, 20].

IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

MONITORING OF GI FUNCTION AND IAP

Because GI function is difficult to "measure" and quantify, this topic has been under-investigated and neglected in the past. Definitions of symptoms reflecting GI function have been proposed by the Working Group on Abdominal problems of ESICM (European Society of Intensive Care Medicine) aiming to standardise definitions and thereby improve the quality of future research [7]. Even with standardised definitions of GI symptoms, clinical examination remains subjective and, therefore, not accurate enough to monitor GI function. However, the already-provided descriptive characterisation of Acute Gastrointestinal Injury (GI dysfunction as a part of MOF) should assist with contextual support [7].

Although biomarkers for the evaluation of GI dysfunction have been studied, none of them has yet made its way to clinical practice. Citrulline is considered a marker of functional enterocyte mass. A reduced citrulline level is associated with critical illness, GI dysfunction [115], IAH and increased mortality [116]. As citrulline concentrations are influenced by renal function, the practical value in critically ill patients is questionable.

The intestinal fatty acid binding protein (I-FABP) is a fast marker of intestinal ischaemia/cellular damage [117]. I-FABP is largely independent of underlying co-morbidities and may help distinguish sepsis of intestinal origin from other forms of sepsis [118, 119].

FLUID MANAGEMENT IN IAH AND GI DYSFUNCTION

Although hypovolemia needs to be corrected, at the same time great attention should be paid to avoid fluid overload in both in IAH and GI dysfunction. As soon as hemodynamic stability is achieved after the resuscitation phase, there should be a transition to a more conservative fluid management and a 'late goal directed fluid removal' (de-resuscitation) [72].

Despite the knowledge that increased volumes of fluid resuscitation increases gut oedema and IAH, the best type of fluid in critically ill patients with impending or established gut oedema and/or IAH is unknown. Although some experimental data suggests the use of colloids over crystalloids as beneficial regarding the development of gut oedema [120], so far no colloid has proven superior to crystalloids in clinical trials [121, 122].

Theoretically, hypertonic saline acts to expand intravascular volume by increasing serum osmolarity, inducing a fluid shift across cell membranes into the extracellular, and then intravascular space along a sodium-driven concentration gradient. Hypertonic saline also has immunomodulatory properties and simultaneously allows for rapid restoration of the circulating intravascular volume with fewer administered fluids. However, the risk of hypernatremia needs to be considered while current data do not allow evidence-based recommendations.

MECHANISMS AND THEORIES TO BE EXPLORED AND CLARIFIED IN FUTURE STUDIES

THEORY I: ROLE OF THE GI SYSTEM IN MOF

Although the concept of the gut as the motor of critical illness has been around for decades, the theory behind it has become much more complex during this time. The initial theory of bacterial translocation as the single/main mechanism has not been supported enough in the studies [93], and other concomitant mechanisms have been suggested. Nowadays, changes in microbiota together with erosion of the mucus barrier and damaged gut integrity, the formation of toxic lymph in the gut, as well as simultaneous dysregulation of epithelial proliferative and apoptotic response are all thought to occur in the cascade. This cascade, rather than one single component of it, leads to systemic injury driving critical illness. The question remains as to how to stop this vicious circle of mechanisms amplifying and recommencing anew.

THEORY II: GI DYSFUNCTION AS A PART OF MOF

Currently, the GI system is not included in the assessment of multiple organ dysfunction syndrome. The pathophysiological rationale and clinical data support the need incorporating GI dysfunction as a part of MOF [4, 8].

THEORY III: ROLE OF IAP IN DEVELOPMENT OF MULTIPLE ORGAN FAILURE

IAH occurs in about 40% of the ICU population within the first week of ICU stay. More than half of these patients present with IAH grade I and approximately one quarter with IAH grade II [24]. Most studies confirm the association of IAH and poor patient outcome [11]. However, some authors suggest that mortality is not increased by IAH when corrected by other confounding factors [19]. Arguably, the degree of IAH may only be a marker of disease severity. Indeed, patients with IAH often present with higher severity of illness scores, which itself may contribute to a longer duration of mechanical ventilation and longer ICU and hospital stays [20]. The isolated impact of IAH (considering also its severity and duration) on organ dysfunctions and mortality is, therefore, not yet completely clarified.

THEORY IV: GI DYSFUNCTION AS A REASON FOR IAH

GI pathology/dysfunction leading to increase in IAV usually increases IAP. Bowel oedema and bowel distension are probably the most important pathophysiological conditions that need to be considered in critically ill patients. It is unclear whether, and to what extent, the negative impact of these pathophysiological conditions on patient outcome is further increased by IAH. The assessment of these pathophysiological conditions is limited to direct evaluation during surgery and radiological imaging, whereas monitoring of IAP is the only dynamic surrogate marker that should be applied in all patients with bowel oedema or distension.

THEORY V: GI DYSFUNCTION AS A RESULT OF IAH

An increase in IAP directly impacts the GI tract. A few studies have shown that GI symptoms occur more often in patients with IAH and that IAH is associated with feeding intolerance. However, this causative relationship is still not fully understood.

CONCLUSIONS

As GI dysfunction and IAH share one compartment and multiple pathophysiological mechanisms, they should be seen and treated as an inseparable couple. While exact interactions between GI function and IAP still need to be clarified, GI dysfunction can lead to IAH and vice versa. Therefore, monitoring of IAP is strongly recommended in critically ill patients with Acute Gastrointestinal Injury (GI dysfunction as a part of multiple organ dysfunction syndrome).

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